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Renal ischemic preconditioning: finally some good news for prevention of acute kidney injury

Zoltán H. Endre[1,2]

Recent clinical trials of remote ischemic preconditioning offer hope that this well-validated experimental method of protecting tissues against ischemic injury will provide a more robust alternative to pharmaceutical prevention against cardiac and renal ischemic injury.

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Ischemic preconditioning is an innate tissue adaptation induced by ischemia or toxic insult that confers both local and remote organ protection against subsequent exposure to the same or other injury. Local ischemic preconditioning was first observed in dogs as the limitation of myocardial infarct size produced by a series of brief (4×5 min) circumflex artery occlusions and reperfusions before a more sustained occlusion of the same artery.[1] Later studies identified the existence of remote ischemic preconditioning (RIPC), where transient ischemia of many organs and tissues, including heart, kidney, small bowel, liver, and skeletal muscle, induced systemic multiorgan protection against subsequent extended ischemia–reperfusion injury.[2,3] Ischemic preconditioning is highly conserved across species.[2] RIPC suggests the involvement of humoral mediators, and many experiments demonstrate that protection is dialyzable, transferable, and receptor-mediated.[2,3] The observation that upper- or lower-limb ischemia induced by inflation of a blood pressure cuff provided myocardial protection in the absence of known adverse risks, and that protection could occur after initiation of injury (postconditioning), offers a tantalizing, cheap, and easily applicable strategy for the prevention of acute kidney injury (AKI) in high-risk patients, provided that real clinical benefits are reproducible.

Classically, local ischemic preconditioning induces immediate (early) protection, which wanes after a few hours. Early protection is followed by a delayed phase of protection that appears about 12–24 h after the inducing stimulus. Delayed protection is weaker but usually persists for days.[2,3] RIPC induces similar early and late protection, and both types of preconditioning occur largely through modulation of the response to reperfusion. Nevertheless, there are mechanistic differences between local and remote preconditioning,[2] and the details of signal transduction and effectiveness vary among species and the type of stimulus. Various humoral factors, including adenosine, bradykinin, and cannabinoids, may be involved, and subcellular modulators such as nuclear factor-κB and nitric oxide appear to be involved (Figure 1).[2–4] Interestingly, preconditioning appears to require intact innervation of the preconditioning organ but not the target organ. Similarly, early and late ischemic preconditioning differ in the relative importance of mediators, signal transduction pathways, and end effectors. The final common pathway appears to be a cascade of intracellular kinases with

[1]*Department of Nephrology, Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia and* [2]*Christchurch Kidney Research Group, Department of Medicine, University of Otago, Christchurch, New Zealand*
Correspondence: *Zoltán H. Endre, Department of Nephrology, Prince of Wales Hospital, High Street, Randwick, Sydney, New South Wales 2031, Australia.*
E-mail: Maureen.Sullivan@sesiahs.health.nsw.gov.au

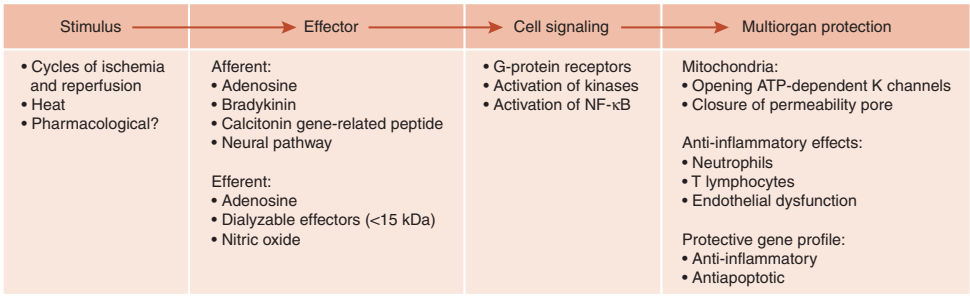

Figure 1 | Remote ischemic preconditioning. Schematic illustration of pathways potentially involved in remote ischemic preconditioning in animal models and humans. Organs in which protection has been observed experimentally include the brain, heart, kidney, liver, and lung. Cycles of ischemia–reperfusion have used upper- and lower-limb ischemia as well as other vascular beds, including the common iliac artery. ATP, adenosine triphosphate; NF-κB, nuclear factor-κB.

subsequent opening of adenosine triphosphate-sensitive potassium channels and closure of the mitochondrial permeability pore (Figure 1).[5] RIPC also induces systemic anti-inflammatory effects and reduces endothelial dysfunction, which may contribute to multiorgan protection.[2]

It has been known for almost a century that prior injury protects the kidney against subsequent injury,[5] with recent studies highlighting modulation of inflammation in ischemic renal preconditioning.[6] Nevertheless, most studies of RIPC have focused on the protection of the organs undergoing direct ischemia–reperfusion injury, such as the heart and lungs in cardiopulmonary bypass surgery, and kidneys in aortic surgery.[7] However, the systemic multiorgan protection offered by RIPC, including induction of anti-inflammatory and anti-apoptotic gene profiles, suggests potential benefit in prevention of AKI during cardiopulmonary bypass. Indeed, RIPC has shown renal-protective effects in major vascular surgery or interventions without direct interruption of perfusion to the kidneys.[7] Nevertheless, renal protection has not been universally observed,[8] although problems arise when the assessment of renal dysfunction is an add-on to studies focused on cardiac function. For example, Rahman *et al.*[8] assessed renal function only 4 days after surgery, which was too late to detect mild to moderate renal dysfunction.

A number of studies have now addressed renal protection as a primary outcome following RIPC. Firstly, Venugopal *et al.*[9] performed a secondary analysis of renal outcomes of two randomized placebo-controlled trials of RIPC for myocardial protection, which used three 5-min cycles of arm ischemia followed by reperfusion in 78 patients undergoing cardiac surgery. This retrospective analysis showed a reduction in the incidence of stages 1, 2, and 3 of AKI by the AKI Network (AKIN) criteria from 25, 0, and 0% in the control to 3, 8, and 0% in the RIPC group. Secondly, a prospective randomized double-blind controlled trial of RIPC by Choi *et al.*[10] used three 10-min cycles of lower-limb (thigh) ischemia and reperfusion in 76 patients undergoing complex valvular cardiac surgery. The primary outcomes were AKI incidence (AKIN definition) and changes in plasma cystatin C at 24 and 48 h after bypass and in the renal injury biomarker plasma neutrophil gelatinase-associated lipocalin (NGAL) at 24 h after bypass. There were no differences in incidence of AKI (12/38 in control and 14/38 in RIPC group) or in the concentrations of renal injury biomarkers between the two groups, although there was a decrease in the creatine kinase MB fraction and in the length of intensive care unit stay in the RIPC group, supporting cardiac benefit.

Zimmerman *et al.*[11] (this issue) report a randomized single-blind controlled pilot study of RIPC that used three 5-min cycles of lower-limb (thigh) ischemia and reperfusion in 120 patients undergoing cardiopulmonary bypass surgery. The primary outcome was the incidence of AKI (AKIN definition), and the secondary outcomes included change in plasma NGAL 3 h after bypass. There was an absolute risk reduction in AKI of 0.27 (95% confidence interval, 0.10–0.42) with a change in incidence from 28/59 (47%) in the control to 12/59 (20%) in the RIPC group ($P=0.004$). *Post hoc* analysis of the latter study also showed a reduction in both stage 1 and stage 2 grades of injury versus controls (there were no stage 3 patients in either group). There was also a reduction in the incidence of AKI sustained for at least 2 days in the RIPC group ($P=0.04$). As with the previous study,[10] there was no difference in the change in plasma NGAL levels between the two groups.

What conclusions are we to draw from the two prospective studies? Firstly, both should be considered pilot studies, as they are underpowered to assess RIPC as a therapeutic intervention. The overall incidence of AKI, by the same definition of AKI, was greater in control subjects in the study by Zimmerman *et al.*[11] (47%) than the overall incidence in the study by Choi *et al.*[10] (37%), suggesting differences in the propensity scores for AKI, although the control and RIPC groups were well matched within each study. This reflects the exclusion of patients with preexisting renal dysfunction by Choi *et al.*[10] That study observed evidence for myocardial protection and reduced length of intensive care unit stay as tangible benefit in the RIPC group. Surprisingly, length of intensive care unit stay appeared the same in the control and RIPC groups in the study by Zimmerman *et al.*[11] despite the massive reduction in AKI incidence in the RIPC group. It is not clear whether the detection of stages 1 and 2 AKI was a factor in guiding clinical management in that study despite a growing literature suggesting that even small increases in creatinine are associated with adverse short- and long-term outcomes. As change in cardiac biomarkers was not reported, it is unclear whether there was cardiac protection from RIPC in the study by Zimmerman *et al.*[11] No patients requiring dialysis (AKIN stage 3) were reported in either study, so neither offers insight into the effect of RIPC on severe AKI.

Absence of severe AKI may also explain why plasma NGAL did not detect AKI in either study. With less severe AKI in the low-risk cohort in the study by Choi *et al.*,[10] any increase in this relatively short-lived

AKI biomarker would have normalized within 24 h when sampling was performed. An alternative explanation is that the performance of all urinary biomarkers, including NGAL, is reduced and delayed in patients with chronic kidney disease (CKD).[12] Our analysis of plasma NGAL data in the EARLYARF study[12,13] showed a similar dependence of performance on baseline renal function and duration of injury to the urinary markers (unpublished data). Thus, although Zimmerman *et al.*[11] collected NGAL data at the potentially optimal time of 3 h after bypass, that time is not optimal for patients with CKD! Thus inclusion of patients with baseline CKD has the effect of creating a more realistic but also more heterogeneous population from a biomarker perspective. Stratifying for baseline renal function would require a much larger number of patients. For these reasons, the NGAL results were unhelpful in both studies in detecting renal injury independently of change in serum creatinine.

Overall, the results of RIPC in these two studies[10,11] appear consistent with the propensity for development of AKI in the patient cohorts studied. The lower the expected incidence of AKI, the larger the study required to assess renal protection. CKD is a well-known risk factor for AKI and is present in approximately 30% of cases. We should therefore be encouraged by the outcome in the more realistic population in the Zimmerman *et al.* pilot study in patients reported here,[11] in which 16% had underlying CKD (estimated glomerular filtration ate <60 ml/min/1.73 m^2). Nevertheless, the dose and type of ischemic preconditioning needed are not yet established, and the effects of age, drugs, and comorbidity on the response to RIPC await validation in much larger multicenter studies. It remains to be seen whether renal protection is independent of improving myocardial function with RIPC.

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Immunosuppressive treatment of focal segmental glomerulosclerosis: lessons from a randomized controlled trial

Jeroen K.J. Deegens[1] and Jack F.M. Wetzels[1]

Patients with steroid-resistant focal segmental glomerulosclerosis (FSGS) may benefit from treatment with calcineurin inhibitors. A National Institutes of Health–funded FSGS multicenter study has suggested that a combination of mycophenolate mofetil and oral dexamethasone pulses was equivalent to cyclosporine. However, since the study was underpowered, one cannot draw firm conclusions from this study. The FSGS trial underscores that FSGS is not one disease and that better predictors of outcome and response to therapy are needed.

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Focal segmental glomerulosclerosis (FSGS) is one of the most common patterns of glomerular injury and an important cause of end-stage renal disease in both adults and children. FSGS can be idiopathic (with unknown cause) or secondary (with underlying cause).[1] In recent years, many new causes of FSGS have been identified. The prognosis of FSGS is predicted by the severity and persistence of proteinuria, with 60% of patients with persistent nephrotic-range proteinuria progressing to end-stage renal disease within 5–10 years.[2] Achievement of a remission, whether spontaneous or induced by immunosuppressive therapy, is associated with a good outcome.[1]

Although there is no evidence from randomized controlled trials, corticosteroids

[1]*Department of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*
Correspondence: *Jack F.M. Wetzels, Department of Nephrology 464, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: j.wetzels@nier.umcn.nl*